DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/02/2010 has been entered.

Claims 76, 79-82, 90, 91, 99, 100 and 141-144 are being examined.

Response to Arguments

Applicant's arguments filed 12/02/2010 have been fully considered but they are not persuasive.

The declaration under 37 CFR 1.132 filed 12/02/2010 is insufficient to overcome the rejection of claims 76, 79-82, 90, 91, 99, 100 and 141-142 based upon insufficiency of disclosure under 35 U.S.C. 112, first paragraph as set forth in the last Office action because: The declaration and accompanying arguments did not fully address the elements of unpredictability in the art upon which the scope of enablement rejection was based (see below).

In applicant's remarks, applicant cites the declaration of coinventor Dr. C. Pachuk, who states "...it is clear that when dsRNA molecules are administered intracellularly there is generally little or no stress response observed, while the same dsRNA molecules administered extracellularly can induce a much stronger stress

response." Applicant goes on to state "Intracellular expression of a dsRNA molecule in a cell to reduce the interferon response was not known in the art at the time of filing..." If one thing is perfectly clear from the prior art and the prosecution history of this application, it is that RNA stress competent cells undergo a well-characterized RNA stress response when exposed to exogenously-administered dsRNA. As long ago as 1969, Colby and Chamberlin (Colby and Chamberlin, The specificity of interferon induction in chick embryo cells by helical RNA; Biochemistry, vol. 63, pp. 160-167, 1969) demonstrated that cells exposed to exogenously administered dsRNA polymers undergo a stress response that is at least partially mediated by cell surface receptors. RNA stress response to exogenous non-viral dsRNAs is utterly predictable. To further clarify the state of the prior art at the time of invention, it was also known that one could predictably express ssRNAs, including antisense RNAs, intracellularly without stimulating a strong dsRNA stress response. For example Der and Lau (Der and Lau, Involvement of the double-stranded-RNA-dependent kinase PKR in interferon expression and interferon-mediated antiviral activity; PNAS, vol. 92, pp. 8841-8845, 1995), express an antisense RNA to the PKR gene in RNA stress competent cells. In fact, the subject matter of Der and Lau is so close to the claimed subject matter of the instant application that it would be used in an obviousness-type prior art rejection if it were not for one thing: the unpredictability in the state of the art at the time of invention with respect to intracellular expression of dsRNAs. **This enablement rejection relates to the unpredictability in the state of the art at the time of invention with respect to intracellular expression of dsRNAs.**

dsRNA stress responses to intracellularly expressed dsRNA molecules were well known in the art at the time of invention. For example Torrence et al. (Torrence et al., Activation of human and mouse 2-5A synthetases and mouse protein P1Kinase by nucleic acids; FEBS Letters, vol. 130, no. 2, pp. 291-296, 1981) describes dsRNA activation of two intracellular dsRNA binding proteins, 2-5 oligoadenylate synthetase and PKR, which have long been known in the art and have been studied extensively. Robertson and Mathews (Robertson and Mathews, The regulation of the protein kinase PKR by RNA; Biochimie, vol. 78, pp. 909-914, 1996) also teach PKR as an intracellular dsRNA binding protein that mediates dsRNA stress responses in RNA stress competent cells. These two prior art references use in vitro methods to analyze the substrate specificity of intracellular dsRNA-binding, but nevertheless teach the longstanding awareness of those of ordinary skill in the art of the existence and activity of such dsRNA-binding molecules inside of cells. Two postfiling publications also help reflect the state of the art near the time of invention. Saunders and Barber (Saunders and Barber, The dsRNA binding protein family: critical roles, diverse cellular functions; The FASEB Journel, vol. 17, pp. 961-993, 2003) and Tian et al. (Tian et al., The double-stranded RNA-binding motif: interference and much more; Nature Reviews, vol. 5, pp. 1013-1023, 2004) list 15 dsRNA binding proteins expressed in human cells. These references demonstrate that it was well known in the art at the time of invention that RNA stress competent cells contain dsRNA binding proteins that are capable of activating the dsRNA stress responses, and they also demonstrate that much was not understood at the time of invention and disclosure about how these dsRNA binding molecules function, their dsRNA binding specificity, their intracellular targets and their mechanism of action. It

would be an understatement to say that there was much uncertainty and unpredictability in the art at the time of invention regarding cellular RNA stress responses to intracellularly expressed dsRNA. Once again, in view of the foregoing, it is due in part to the complexity of the RNA stress response pathways and the unpredictability in the art at the time of invention that the disclosure of the instant application is not enabling.

Continuing with applicant's arguments, on pages 6-9, applicant discusses previously cited postfiling references Robbins et al., Kenworthy et al., and Bauer et al., asserting that interferon responses are predictably low in some experimental conditions. Some aspects of these arguments are moot in light of applicant's amendments; rather than claiming 'does not induce a detectable RNA stress response', applicant now claims a 20% decrease in apoptosis relative to extracellularly transfected dsRNA, and so details as to the presence or absence of low levels of immune responses are no longer relevant. Note also that none of these three references discusses RNA stress responses in the context of comparisons with extracellularly transfected dsRNA, and a review of the literature reveals little interest in the question of comparing the responses of cells to intracellularly expressed versus extracellularly transfected dsRNA. As noted in the 112 2nd paragraph rejections, it is also problematic to establish a standard of comparison for intracellularly expressed versus transfected dsRNA, which could partially account for the prior art's silence in this area.

Despite the changes in the claims, applicant's arguments with respect to the Robbins, Kenworthy and Bauer references are still not persuasive relative to the question of enablement and addressing the level of uncertainty in the art. Taking for example Robbins et al., as it has already been introduced and discussed at length in this case,

applicant asserts that Robbins shows no immune response for a set of highly optimized siRNAs specifically designed to avoid immune responses in human cells (p. 6, paragraph 1 of applicant's response). However, Figure 3a and 3b in Robbins clearly show immune responses of shRNAs several-fold above control levels. In many contexts, for instance biomarker analysis or gene expression studies, a two-fold response is considered a 'significant' response. While immune responses are typically many-fold higher, certain elements of RNA stress responses have not been abolished in these cells. The precise levels of stress responses are no longer relevant in light of applicant's amendments, but predictability is. Robbins exemplifies that even in an experimental system which has been extensively optimized to avoid immunogenicity, certain elements of intracellularly expressed dsRNA stress responses continue to be unpredictable. Similar to Robbins, references Kenworthy and Bauer teach very different strategies for evading RNA stress response than those taught by applicant, and the existence of even low levels of unpredictability in these highly-optimized systems reveals what those of ordinary skill in the art understand, namely that RNA stress responses in response to dsRNAs, even those extensively optimized for non-immunogenicity, can and do occur. As above, applicant's arguments regarding the fact that Bauer did not measure stress response to extracellularly transfected dsRNAs (p. 8 last paragraph, Dr. C Pachuk quote) is not relevant to the question of predictability, because the element of predictability that is germane to the enablement rejection is the predictability of RNA stress response due to intracellular dsRNA expression.

Applicant concludes by observing that '...methods to identify dsRNA effector sequences that work have been, and are used routinely by those of skill in the art in a

number of contexts and therefore do not present an undue burden.' (p. 10, line 20) With respect to the question of whether applicant's disclosure, in combination with the prior art available at the time of disclosure enabled persons of ordinary skill in the art to practice the invention, it should be noted that many individuals contributed to our present day understanding of how dsRNAs may be utilized to silence genes. The references cited in this action, in previous action, and the references cited by applicant speak to a state of the art that was in flux at the time of applicant's disclosure and in which there was considerable uncertainty as to the mechanism and predictability of immune responses to dsRNA. Applicant's disclosure must be evaluated in the context of the art, and at the time of disclosure the art was in the midst of a massive collective effort to dissect the mechanisms of dsRNA-mediated gene silencing in human and non-human cells alike. In that context applicant and persons of ordinary skill in the art were aware of the level of uncertainty surrounding individual observations. Applicant's assertion that through the invention applicant 'improved the predictability' of downregulating genes via dsRNA is certainly true, as it was generally regarded as impossible to use long dsRNAs to downregulate genes in human cells prior to applicant's invention. However, as described below in the 112 1st paragraph rejection, applicant's disclosure does not rise to the level of enabling others of ordinary skill in the art to practice the invention commensurate in scope with the claims. There was simply too little guidance provided in the disclosure and too much unpredictability in the art at the time of disclosure for the invention to be enabling beyond the single example provided. A great deal of additional effort and experimentation was required on the part of many individuals to identify circumstances under which dsRNA inhibition of gene expression could be carried out with any measure

of predictability, and applicant's assertion that their disclosure supports generic coverage for all intracellularly expressed dsRNAs is not credible.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 76, 79-82, 90, 91, 99, 100, 141-144 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for silencing of PSA using a 600 nt dsRNA in rhabdomyosarcoma cells, does not reasonably provide enablement for gene silencing of other genes, using other constructs, in other cell types. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

This is a new rejection necessitated by amendment.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The invention is a method of silencing gene expression using intracellular expression of dsRNA in RNA stress competent cells without fully stimulating immune responses.

Breadth of the claims. All gene silencing by intracellularly expressed dsRNAs in all RNA stress competent cells is claimed. This includes potential human therapeutic applications as well as cell culture applications.

State of the art. The state of the art continues to be in flux with respect to precise determinants of RNA stress responses from intracellularly-expressed dsRNAs. At the time of invention there was particular uncertainty as to the predictability of RNA stress responses, as use of dsRNAi in mammalian cells was in its infancy.

Number of working examples and Guidance provided by applicant. One working example is provided. Guidance is generic and does not suggest particular cell types in which the method is most likely to be effective, particular promoters or RNA polymerases that are most likely to be effective, or particular lengths or compositions of dsRNAs that will be most likely to be effective. Applicant's guidance as to which genes could be targeted is particularly revealing with respect to applicant's assessment of the predictability in the art at the time of invention. In Example 7, applicant's guidance suggests using dsRNAs to target genes involved in cellular immune responses to dsRNA. While applicant does not provide guidance as to how or if targeting these genes with dsRNA is likely to work, this guidance does serve to inform one of ordinary skill in the art that applicant does not believe that administration of dsRNAs by intracellular expression will predictably evade immune responses. In fact, in example 7 applicant suggests numerous potential dsRNA stress response targets, in the event that the method

should fail to effectively downregulate PKR, and this is despite the fact that Der et al (cited above) had previously demonstrated that PKR could be downregulated via intracellular expression of antisense RNA. This guidance strongly suggests that applicant, consistent with what was generally known in the art at the time of invention, believed that immune responses to intracellularly expressed dsRNA, while lower than those of exogenously administered dsRNA, would still be an obstacle to practicing the method as disclosed, and that the disclosed experimental results may have been anomalous.

Unpredictability of the art and Amount of experimentation required. There was and is significant unpredictability in the art of expressing dsRNAs in RNA stress response competent cells. Numerous disclosures support this conclusion: Before applicant's disclosure Bahramian (Bahramian et al., Transcriptional and Posttranscriptional Silencing of Rodent a1(I) Collagen by a Homologous Transcriptionally Self-Silenced Transgene; Molecular and Cellular Biology; vol 19, no. 1, pp. 274-283, 1999) described silencing of the collagen gene by an RNA transgene and identified regions of the gene that were critical to silencing. Bahramian was unable to account for this observation, despite the fact that expressing transgenes was well known in the art; Bahramian even speculated that this silencing mechanism could have been related to the RNAi mechanisms that had been identified in non-RNA stress competent cells. After applicant's disclosure Billy et al. (Billy et al., Specific interference with gene expression induced by long, double-stranded RNA in mouse embryonal teratocarcinoma cell lines; PNAS, vol. 98, no. 25, pp. 14428-14433, 2001) and Yang et al. (Yang et al., Specific Double-Stranded RNA Interference in Undifferentiated Mouse Embryonic Stem Cells;

Mol Cell Biol, Vol. 21, No. 22, pp. 7807-7816, 2001) described gene silencing with dsRNA. Billy et al. described an inability to silence genes utilizing dsRNA in differentiated cells (i.e. RNA stress-competent cells), but not in ES cells, while Yang et al. described silencing accompanied by partial interferon responses in neuronal cells. Neither of these references supports applicant's assertion that the effects of expressing dsRNAs intracellularly are predictable. In fact, Billy et al. cites several references in which dsRNAs did not specifically silence genes in RNA stress competent cells, further underscoring the unpredictability in the art. Numerous references related to siRNAs cite the tendency of longer dsRNAs to stimulate the immune system as a reason for utilizing shorter inhibitory RNAs for gene silencing. Nevertheless, minimizing immune responses of siRNAs, including endogenously expressed siRNAs, has been discussed extensively in the literature, further demonstrating the unpredictability in the art. For example, Akashi et al., (Akashi et al., Escape from the interferon response associated with RNA interference using vectors that encode long modified hairpin-RNA; Molecular Biosystems, vol. 1, pp. 382-390, 2005) describe a system for expressing long dsRNA while avoiding 'off target' effects brought about by cellular immune responses. Like the disclosure of Billy et al. and Yang et al., Akashi's disclosure reflects the considerable unpredictability of immune responses in RNA stress competent cells in which dsRNA was expressed intracellularly. Managing unpredictable biological responses is extremely important in the biological sciences, and predictability is critical to the widespread adoption of any experimental system. Disclosures like Billy, Yang and Akashi exemplify the type of disclosure which enables practitioners to incrementally advance the art, although none of these teachings would, in and of itself, support claims as broad as

applicant's. Applicant's duty to provide enabling disclosure goes beyond merely stating that those of ordinary skill in the art can manage to grapple with the unpredictability in the art in order to make and use the claimed invention.

In conclusion, while applicant asserts that conditions for silencing genes by dsRNA can generally be identified by persons having ordinary skill in the art, applicant does not disclose those conditions nor does applicant offer guidance as to how one can effectively extrapolate from the disclosed invention to additional cells, constructs or genomic loci. Without that disclosure, the invention is not enabled. In their arguments, applicant suggests that any gene can be silenced with dsRNAs if a skilled practitioner sets out to do so. This may be the case, but by the standards of the art, applicant's disclosure falls far short of being enabling. The disclosure of the instant application is so scant that a skilled practitioner would avoid utilizing such a disclosure as guidance for how to make and use such an invention. It offers only the most general of suggestions, recapitulates what was known in the art (i.e. example 7, which reflects applicant's expectation that unpredictability of immune responses would be a problem with intracellularly expressed dsRNAs) and, as such, is not enabling to one of ordinary skill in the art beyond what is explicitly outlined in the disclosure: silencing of PSA, using a 600 bp dsRNA in rhabdomyosarcoma cells.

Claims 76, 79-82, 90, 91, 99, 100, 141-144 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims a method of introducing a vector encoding dsRNA into cells in order to downregulate gene expression. The claims read on a broad genus of RNAi methods.

The written description requirement for a genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicants were in possession of the claimed invention. In the instant case, the specification does not sufficiently describe a representative number of methods for downregulating gene expression via dsRNA by actual reduction to practice or by disclosure of relevant identifying characteristics.

The state of the art at the time of filing does not provide sufficient information on the subject to overcome the deficiencies of the instant specification. There is no description in the art that allows one to envision a representative number of dsRNAi constructs by disclosing structural or functional features of dsRNAi constructs so that one of skill in the art could envision the claimed invention. Thus the skilled artisan cannot consult the art at the time of filing to envision a sufficient number of embodiments of the instant invention to see that the applicant was in possession of the claimed genus.

Neither the specification of the instant application or the state of the art at the time of filing teaches a structure-function relationship for a representative number of dsRNAi constructs capable of downregulating genes in RNA stress competent cells. As a result, the skilled artisan would not be able to envision the claimed invention. Therefore

applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

Claim 76 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new matter rejection necessitated by amendment.

The claimed 20% reduction in apoptosis of an RNA expressed intracellularly compared to the same RNA transfected externally is new matter that is not supported by the specification. No disclosure is made as to what RNA was utilized for transfection, how this RNA sequence compares to the intracellularly expressed RNA, what concentrations of RNA were to be utilized or under what experimental conditions the comparison was to be made. Moreover, no mention is made of directly comparing intracellularly versus extracellularly administered RNA. Without this disclosure the amendment is not supported by the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ADDISON D. AULT whose telephone number is (571)270-7028. The examiner can normally be reached on Monday-Friday: 8-4:30 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571)272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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